HIV-infected patients with community-acquired pneumonia in a tertiary teaching hospital

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ABSTRACT

Background: Bacterial pneumonia is one of the main causes of morbidity and mortality in patients infected by the human immunodeficiency virus (HIV). The main objective of this study was to evaluate the effect of macrolide therapy in combination with a beta-lactam based empiric regimen for inpatients with community-acquired pneumonia and HIV. **Methods:** This is a retrospective cohort study of hospitalized patients. Adult patients who had received treatment with ceftriaxone or ceftriaxone plus clarithromycin were included. **Results:** 76 patients met the inclusion criteria. Among baseline characteristics analyzed, only respiratory rate showed significant difference: patients who had received clarithromycin were more likely to have a respiratory rate > 30/min than patients who received only ceftriaxone (64% *versus* 36%, p = 0.03). ICU admission was the only outcome that showed a significant difference, more frequent in the ceftriaxone plus clarithromycin group (45% *versus* 20%, p = 0.03). **Conclusions:** This study does not support the addition of a macrolide to a beta-lactam based regimen in HIV-infected patients. This is probably related to the patients' immunodeficiency status, which impairs the immunomodulatory properties of the macrolides.

Keywords: HIV; pneumonia; macrolides; mortality.

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INTRODUCTION

Bacterial pneumonia is one of the main causes of morbidity and mortality in patients infected by the human immunodeficiency virus (HIV).[1,2] Its incidence has decreased after the introduction of highly active antiretroviral therapy (HAART);[3,4] however, these patients still have a higher risk of acquiring this type of infection, when compared to the general population,[3] in addition to having higher rates of invasive pneumococcal disease[5] and mortality.[6,7]

The etiology of community-acquired pneumonia (CAP) in HIV-infected patients is similar to that of immunocompetent patients, with the main agent being *Streptococcus pneumoniae*. Infections by Gram-negative bacteria (including *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Legionella pneumophila*, among others) are common, as well as by *Staphylococcus aureus*.[1,2,3,6]

The following are considered risk factors for CAP in HIV-infected patients: low socioeconomic level, smoking, alcohol consumption, use of intravenous (IV) drugs, comorbidities (including cardiovascular disease, kidney disease or liver cirrhosis), malnutrition, low CD4+ T-cell counts (CD4 < 200 cells/μL), HIV replication and lack of HAART.[2]

Regarding prevention, the role of the antipneumococcal vaccine in HIV-infected patients is yet to be defined, as the studies have shown controversial results.[8,9] Moreover, prophylaxis with sulfamethoxazole-trimethoprim (SMX-TMP) is a disputable question, as it seems to prevent bacterial pneumonia only in patients who are not on HAART.[1,3]

To date, some proposals have been made regarding the severity assessment of a pneumonia episode in an HIV-infected patient; however, none of them have been validated in this group of patients.[2] The Pneumonia Severity Index (PSI) consists of interesting rules that can predict mortality in HIV-infected patients.[10] Another interting severity score is the CURB-65, adopted by the Brazilian Consensus of CAP due to its simplicity[11] (patients are considered severe when they have a score of IV or V at PSI or a score 3 at CURB-65).

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Another strategy to predict severity is to combine the scores with the CD4 count, as patients with CD4 counts < 200 cells/μL have higher mortality. Therefore, patients with CD4 < 200 cells/μL or high severity scores would be considered severe cases.[2,10]

Patient severity assessment is important for decision-making regarding the type of treatment and where the latter must be carried out. In fact, choosing the empiric treatment for bacterial pneumonia in HIV-infected patients is a great challenge, as most studies and consensus are directed at immunocompetent patients.

Moreover, the studies that deal with the choice of empiric therapy for CAP are heterogeneous regarding the compared regimens, the population included in the study, and the analyzed outcomes. Some studies have a group of patients with immunodeficiencies, but none of them particularly assessed HIV-infected patients.[12-14]

There is evidence of decreased mortality in patients treated with hospital-based regimens that included the combination of beta-lactams and macrolides, when compared to other regimens.[14] Other studies have demonstrated benefits with regimens that contain macrolides, when compared to regimens without this class of antibiotic agent.[12,15] Additionally, the benefit of combined therapy over monotherapy have been demonstrated.[13]

Considering that, to date, there is no consensus regarding the best empiric therapy for HIV-infected patients admitted to the hospital due to CAP, this study was carried out with the objective of assessing the impact of combining a macrolide to the beta-lactam therapy in this population. For that purpose, the primary outcome analyzed was mortality during hospital stay.

METHODS

This a retrospective cohort study of adult HIV-infected inpatients with CAP admitted to *Instituto de Infectologia Emílio Ribas*, a tertiary teaching hospital in the city of São Paulo, state of São Paulo, Brazil.

Records of patients older than 18 years, admitted from January 1st, 2007 to December 31st, 2007, were selected for the study. Were reviewed the records of patients that had on admission a primary diagnosis of HIV-infection (CID-10: B20-B24) and a secondary diagnosis of pneumonia (CID-10: J10 to J18.9) or vice-versa. For patients admitted more than once during the study period, only the first hospitalization was considered.

Patients that had at least one symptom of acute lower respiratory tract disease at admission (coughing, expectoration, dyspnea or chest pain) and who received CAP-directed therapy consisting of ceftriaxone or ceftriaxone plus clarithromycin, initiated within 24 hours of admission, were included in the study.

Exclusion criteria were: (I) hospital admission during the 14-day period prior to admission; (II) diagnosis of tuberculosis or starting empiric treatment with anti-tuberculosis agents within the first 24 hours after admission; and (III) CAP-directed therapy consisting of antibiotic agents other than ceftriaxone and/or clarithromycin. It is noteworthy that patients who received empiric treatment for pneumocystosis were not excluded from the study.

With the objective of characterizing and comparing the two study groups, the following information was obtained from the patients' records: demographic characteristics (age, sex, resident in public shelter, support or retirement home), habits and addictions (smoking, IV drug use, inhaled drug use), data regarding the HIV (use of HAART, CD4, anti-pneumococcal vaccine, prophylaxis with SMX-TMP), presence of comorbidities (neoplasms, liver disease, heart failure, systemic arterial hypertension, previous cerebrovascular accident, previous neurotoxoplasmosis, diabetes, kidney disease) and admission data: clinical [mental confusion, respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), body temperature (BT), heart rate (HR), pleural effusion], radiological (multilobar infiltrate or pleural effusion) and laboratory data (pH, urea, sodium, glucose, hematocrit, PaO_2, $satO_2$).

The demographic data regarding the habits and addictions, related to the HIV-infection and comorbidities were obtained from information registered in the records as a whole. CD4 measurements were considered as those obtained during hospitalization or up to three months before the admission date. Ex-smokers or ex-drug users were considered as addicted to these substances. No data on alcohol use were obtained.

The primary outcome studied was mortality during hospital stay and the secondary outcomes were: admission to the intensive care unit (ICU), total hospitalization and ICU length of stay.

Statistical analysis

Comparisons between groups were carried out by Chi-square test for categorical variables and two-tailed Student's *t* test for continuous variables. The p-values < 0.05 were considered statistically significant. The analyses were performed using the softwares Microsoft O ce Excel 2007 and EpiInfo release 3.5.1.

RESULTS

A total of 251 admissions were reviewed and out of these, 223 cases were selected, as only the first admission in the period was considered for the study.

A total of 132 patients were excluded: 16 had a hospital admission up to 14 days prior to hospitalization, 30 had a diagnosis of tuberculosis or were put on empiric therapy for tuberculosis within 24 hours of admission, 36 did not receive an antibiotic agent within the first 24 hours of ad-

mission, and 50 received CAP-directed therapy with other antibiotic agents. Additionally, 15 cases were not included (two had the antibiotic regimen withdrawn within the first 24 hours of admission, one was transferred to another hospital, and 12 records could not be located).

Thus, 76 patients met the inclusion criteria and were included in the present study. Table 1 shows patient characteristics, grouped according to the therapy they received: monotherapy with ceftriaxone (54 patients) or combined therapy with ceftriaxone and clarithromycin (22 patients).

There was no statistical difference between the groups regarding age, sex, type of housing, habits, addictions and radiological findings (data not shown). Likewise, data regarding the HIV infection and laboratory tests were not different between the groups. Information regarding anti-pneumococcal vaccine was not available in the records.

On physical examination, only respiratory rate (RR) was significantly different: more patients on macrolide (64%) had a RR > 30 ipm than patients on ceftriaxone alone (36%) [p = 0.03].

The frequency of the association with SMX-TMP was similar between the two groups: 41% in patients who received ceftriaxone and 50% in patients who received ceftriaxone and clarithromycin.

The patients were stratified regarding severity using the PSI and CURB-65 scores. In the group of patients who received ceftriaxone, 34 had the necessary information for classifying according to PSI and 8 of them (23%) were considered severe cases. In this same group, 52 patients were classified using the CURB-65 score and of these, 6 (11%)

Table 1. Characteristics of patients who received treatment for community-acquired pneumonia with ceftriaxone* vs. *ceftriaxone plus clarithromycin

	Ceftriaxone	Ceftriaxone + clarithromycin	p
Patients, n	54	22	
Demographic data			
Age	40.2+-10.0	44.9+-11.1	0.11
Male sex	35 (64.8)	16 (72.7)	0.50
Resident of shelter, support or retirement home	2 (3.7)	1 (4.5)	0.86
HIV-related data			
Irregular ARVT	15/43 (34.8)	3/17 (17.6)	0.19
CD4 < 200	25/35 (71.4)	10/15 (66.7)	0.74
Prophylaxis with SMX-TMP	9 (16.7)	3 (13.6)	0.80
Physical examination			
Mental status alteration	3 (5.6)	0	0.26
RR > 30 ipm	19/53 (35.8)	14/22 (63.6)	0.03*
SBP < 90 mmHg	7 (12.9)	3 (13.6)	0.94
BT < 35°C or > 40°C	0/47	1/20 (5.0)	0.12
HR > 125 bpm	9 (16.7)	2 (9.1)	0.39
Laboratory findings			
pH < 7.35	3/45 (6.7)	1/20 (5.0)	0.80
Urea > 65 mg/dL	11/53 (20.7)	3/21 (14.3)	0.52
Sodium < 130 mEq/L	5/52 (9.6)	1/20 (5.0)	0.53
Glucose > 250 mg/dL	1/50 (2.0)	1/20 (5.0)	0.50
Hematocrit < 30%	16/53 (30.2)	4/22 (18.2)	0.28
pO_2 < 60 mmHg	18/45 (40.0)	11/20 (55.0)	0.26
Association with SMX-TMP	22 (40.7)	11 (50.0)	0.46

Data are presented as mean ± standard or n (%). In cases that had missing data, the total number of patients included is shown after the symbol "/". RR, respiratory rate; ipm, incursions per minute; SBP, systolic blood pressure; BT, body temperature; HR, heart rate; pO_2, oxygen arterial pressure; ARVT, anti-retroviral therapy; SMX-TMP, sulfametoxazol-trimetoprim.

Table 2. Outcomes of patients who received treatment for community-acquired pneumonia with ceftriaxone* vs. *ceftriaxone plus clarithromycin

	Ceftriaxone	Ceftriaxone + clarithromycin	p
Patients, n	54	22	
Death during hospitalization	7 (13)	2 (9.1)	0.63
ICU admission	11 (20.4)	10 (45.5)	0.03*
ICU stay duration (days)	11.82 ± 7.44	7.8 ± 6.66	0.21
Time of hospitalization (days)	16.39 ± 15.35	14.86 ± 14.23	0.68

Data are shown as mean ± SD or n (%). ICU, intensive care unit.

were considered severe cases. In the group of patients that received ceftriaxone and clarithromycin, 8 of the 16 patients (50%) classified according to PSI score and 4 of the 21 patients (19%) classified according to the CURB-65 score were considered severe cases. There was no significant difference between the groups.

Table 2 shows the comparison between the two study groups regarding outcomes. There was no significant difference regarding mortality during hospital stay. Among the studied secondary outcomes, only admission to the ICU was significantly different, being more common in the ceftriaxone group (45%) than the clarithromycin group (20%) [p = 0.03].

Analyses were repeated, after excluding the patients who received SMX-TMP and the results were similar. There was no statistical difference between the groups regarding sex, type of housing, existing comorbidities, habits and addictions, radiological findings, laboratory data, HIV-related information and severity (according to the CURB-65 and PSI scores).

At this second analysis, the patients in the group who received ceftriaxone and clarithromycin were relatively older than those who received ceftriaxone alone (47.0 ± 9.5 yrs *versus* 38.9 ± 10 yrs, p = 0.03).

Similarly to the first analysis, the only physical examination finding that showed a significant difference was RR: patients who received clarithromycin had a higher prevalence of RR > 30 ipm than those who received ceftriaxone alone (54% *versus* 19%, p = 0.02).

Excluding patients who were receiving SMX-TMP, there was no difference regarding the outcomes between the group who received monotherapy with ceftriaxone and the group who received combined therapy with ceftriaxone and clarithromycin.

DISCUSSION

This is the first study carried out with the objective of assessing the effect of adding macrolides to beta-lactam therapy in HIV-infected patients.

Of all variables analyzed, only RR was different between the groups: RR > 30 ipm was more prevalent in the group who received ceftriaxone and clarithromycin. Among the studied outcomes, the observed difference was a higher frequency of ICU admissions in the group who received ceftriaxone and clarithromycin.

Although the patients did not have any difference regarding the classification using the severity scores (CURB-65 and PSI), the higher frequency of tachypnea at the physical examination might have been a cause of the higher rate of ICU admissions in the group that received ceftriaxone and clarithromycin.

Several studies that assessed the general population have shown a decreased mortality in patients with CAP, after the addition of macrolides to therapy.[12,14,15] This finding was not supported by the results of the present study, which included only HIV-infected patients.

A Spanish study, carried out in 2003, assessed patients with bacteremia due to *S. pneumoniae* (without excluding HIV-infected patients) and demonstrated a lower mortality during the hospital stay in the group that received beta-lactam plus macrolide (p = 0.001).[14] In this study, the patients who had not received macrolide, had a higher incidence of comorbidities, particularly HIV and malignant hematological diseases (p = 0.0002). However, the percentage of patients with HIV infection among the studied subjects was not reported neither was this group of patients analyzed separately.[14]

The multicentric (international) and prospective study carried out in 2004, with the objective of assessing the effect on mortality of the combination of antibiotics in patients with bacteremia due to *S. pneumoniae*, specified the number of patients with HIV infection in each group. In the group who received combined therapy, 11.4% of the patients had HIV infection and in the monotherapy group, 37.0%; this difference was significant (p < 0.01).[13] A logistic regression analysis demonstrated that even after adjusting for HIV infection, the combined antibiotic therapy maintained a positive association with survival

(*odds ratio*: 0.10; SE 1.7; 95% CI 1.1-9.2; p = 0.028). It is worth mentioning that this study did report which antibiotic classes that comprised the combined therapy were responsible for its superiority.[13]

The reasons why the macrolide can lead to better results in patients with CAP are: antimicrobial synergism, atypical microorganism coverage and immunomodulatory effect. Among these, the most important is the immunomodulation of the inflammatory response and the interference with the pathogenicity of the etiological agent, as there are studies that have demonstrated the benefit of the therapy with macrolides even in patients with microorganisms resistant to this antibiotic class.[15,16]

A North-American retrospective and multicentric study, carried out in 2009, included patients with CAP and severe sepsis and excluded HIV-infected patients. This study demonstrated a lower 30 and 60-day mortality with the use of macrolides, even among patients who had severe sepsis caused by a microorganism resistant to this antibiotic class (hazard ratio: 0.10; 95% CI: 0.02-0.49; p = 0.005).[15]

The immunomodulatory effects of macrolides are yet to be clarified, as there are studies that suggest interference with neutrophil action[16,17] and another study that demonstrates a decrease in pneumolysin production by *Streptococcus pneumoniae*.[18]

A study in particular demonstrates that azithromycin can have a biphasic effect, initially increasing the bactericidal effects of neutrophils and subsequently, when the microorganism has been eliminated, inducing the apoptosis of the latter and interrupting inflammation, leading to a decrease in tissue damage and time of disease.[17]

It has long been known that HIV-infection leads to a qualitative and quantitative neutrophil dysfunction.[19,20] The protection provided by these cells in the presence of bacterial infection is compromised in these patients due to deficiencies in chemotaxis and phagocytosis, free-radical production and altered expression of cell adhesion molecules.[20] There is also an acceleration in the apoptosis process of neutrophils, contributing to the dysfunction and decrease of this cell population.[21]

The population of the present study comprises HIV-infected patients, only. More than two-thirds of the patients in both studied groups had a CD4 count < 200 cells/μL, demonstrating severe immunodeficiency. Therefore, one should expect that in the present study patients a compromised immunomodulatory effect of the macrolide on the neutrophil, in relation to the general population. This might explain why there was no beneficial effect of adding macrolides in this study.

Some limitations of the present study are caused by the retrospective design and, therefore, there are some inherent biases, such as selection errors and missing data. For instance, it was not possible to obtain from the medical records the chest X-ray reports of all cases included in the study, and the radiological alteration was not included as requisite for the diagnosis of pneumonia.

Another important point is the choice criterion between the two types of therapy administered, which was decided by the emergency ward physicians and thus, it was not possible to know which criteria led to the different choices. Nevertheless, we observed that the two groups of patients did not present any differences regarding the proportion of severely-ill patients, according to the classification of severity scores.

As some patients received other types of antimicrobial therapy, we chose to conduct a second analysis, excluding patients that received SMX-TMP and we observed practically the same results.

We conclude that although some studies have suggested the superiority of a beta-lactam plus macrolide regimen when compared to monotherapy with a beta-lactam in the general population, the present study does not lend support to extend this conclusion to HIV-infected patients. This finding is probably related to the patients' immunodeficiency status. Randomized controlled studies, with immunological classification stratification, are necessary to establish the impact of this therapy on the mortality of patients with CAP and HIV infection.

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